REMARKS

A check for the fees for a three-month extension of time accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 06-1050.

Claims 1, 2, 4, 5, 7-10, 18, 19, 50-55, 59-61, 65-72 and 123-127 are pending in this application. Claim 6, 10, 83-86 and 117-122 are cancelled without prejudice or disclaimer. Applicant reserves the right to prosecute cancelled subject matter in continuing applications; cancellation of such subject matter does no indicate that applicant concedes any rejections have merit. Applicant has vigorously argued the propriety of the rejections under 35 U.S.C. §112, first paragraph, and 35 U.S.C. §101 and maintains such arguments. In the interest of advancing some subject matter and claims to allowance, however, the claims have been amended.

Claims 73-82 and 87-116, which are withdrawn from consideration as being drawn to non-elected subject matter, are retained for possible rejoinder. Claim 4 is amended. Amended claim 4 finds basis in original claims 1 and 3. Claims 65 and 69 are amended to clearly recite that the method is a method of screening and that the identified compounds a candidate anti-tumor compounds. Claims 123-127, which are added, find basis in the original claims, including original claims 1, 3, 4, 18 and 65-69. Therefore no new matter is added.

THE REJECTION OF CLAIMS 65-67 and 69-72 UNDER 35 U.S.C. §101

Claims 65-67 and 69-72 are rejected under 35 U.S.C. §101 as allegedly lacking patentable utility for reasons of record. In particular, it is alleged that that the utility of the claimed methods depends upon "disclosure of a specific and substantial utility for a compound discovered," but that there is no specific utility disclosed for such compounds. The Examiner comments are puzzling, since the rejection is predicated on the alleged lack of utility of the identified compounds. It is inconsistent to then urge that case law cited by Applicant in the previous is not relevant because it concerns utility of compounds. Although, as discussed herein, applicant does not agree with the basis for the rejection, the rejection alleges that the application does not provide any specific, substantial utility for any modulator

that might be identified by methods known to the inventors at the time the application was filed. It is further alleged that Applicant has failed to establish that a product found by the claimed methods has utility. The Examiner urges that the specification fails to disclose a specific utility for the products identified by the claimed methods and that, thus, there is no specific utility for the claimed methods. This rejection respectfully is traversed.

Relevant Law

Regardless of the category of invention that is claimed (*e.g.*, product or process), an applicant need only make one credible assertion of specific utility to satisfy 35 U.S.C. §101 and 35 U.S.C. §112; additional statements of utility, even if not "credible," do not render the claimed invention lacking in utility. *See, e.g.*, Raytheon v. Roper, 724 F.2d 951, 958, 220 USPQ 592, 598 (Fed. Cir. 1983), cert. denied, 469 U.S. 835 (1984) ("When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. §101 is clearly shown."); In re Gottlieb, 328 F.2d 1016, 1019, 140 USPQ 665, 668 (CCPA 1964) ("Having found that the antibiotic is useful for some purpose, it becomes unnecessary to decide whether it is in fact useful for the other purposes 'indicated' in the specification as possibly useful."); In re Malachowski, 530 F.2d 1402, 189 USPQ 432 (CCPA 1976); Hoffman v. Klaus, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988). Thus, if applicant makes one credible assertion of utility, utility for any claims are established.

The MPEP provides further guidance to its office personnel that:

> Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations in other cases to mean that products or services based on the claimed subject matter must be "currently available" to the public in order to satisfy the utility requirement. *See, e.g.*, Brenner v. Manson, 383 U.S. 519, 534-35, 148 USPQ 689, 695 (1966). Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility.

Utility under 35 U.S.C.§101 is a minimal threshold issue that can be satisfied by a showing of any use. A small degree of utility is sufficient; an invention must be capable of performing some function that is recognized to be a patentable use, however small, and whether or not it is better at such function than the prior art.

The USPTO has released "Guidelines for Examination of Applications for Compliance with the Utility Requirement" (guidelines) and an "Overview of Legal Precedent

Governing the Utility Requirement" (legal overview) to support the guidelines. Under section I.B.4. of these guidelines Examiners are reminded that,

> "they must treat as true credible statements made by an applicant or a declarant in the specification or in a declaration provided under 37 CFR §1.132, unless they can show that one of ordinary skill in the art would have a rational basis to doubt the truth of such statements."

Further, the legal overview provided by the USPTO, in section II.B.1., explains that, "[a]n applicant's assertion of utility creates a presumption of utility that will be sufficient, in

> most cases to satisfy the utility requirement of 35 U.S.C. §101. ..... To overcome this presumption, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. In other words, the Examiner must show that the asserted utility is not credible." (Emphasis added; see e.g., In re Langer 503 F.2d 1380, 183 USPQ 288 (CCPA 1974).)

The legal overview goes on to explain, in section II.B.2., when an asserted utility is not "credible",

> To assess credibility, the Examiner should determine if one of ordinary skill in the art would consider the assertions of the applicant to have any reasonable scientific basis. If they do, they should not be challenged as not being credible. Only where they do not (e.g., if the assertion is "incredible in view of contemporary knowledge"), should the Examiner challenge the statement as not being credible.

Thus, the Examiner must accept as true any credible statement of utility made by the Applicant and may only challenge the statement upon a showing that those of skill in the art would consider the assertion to have no reasonable scientific basis.

Further there is no requirement that the utility of a pharmacologically active substance be proven by *in vivo* testing. In re Isaacs, 146 USPQ 193, 195 (CCPA 1965). *In vitro* tests can raise the presumption of *in vivo* utility of the claimed compounds. "A standard *in vitro* test may be sufficient to demonstrate pharmacological activity of a compound." Bigham v. Godtfredsen, 222 USPQ 632, 637 (Bd. Pat. App. & Int'f. 1984), see, also Nelson v. Bowler, 206 USPQ 881, 883 (CCPA 1980); and Cross v. Iizuka, 224 USPQ 739, 741 (Fed. Cir. 1985).

With respect to pharmacological and therapeutic utilities, the legal overview provided by the USPTO, in section I.C., interprets Nelson v. Bowler as establishing the following:

> "Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility. ..... These general principles

> are equally applicable to situations where an applicant has claimed a process for treating a human or animal disorder." (Emphasis added.)

The legal overview addresses the analysis of "credibility" of such utilities, in section II.B.2., as follows:

> Special care should be taken when assessing the credibility of an asserted therapeutic utility for a claimed invention. In such cases, a previous lack of success in treating a disease or condition, or the absence of a proven animal model for testing the effectiveness of drugs for treating a disorder in humans, should not, standing alone, serve as a basis for challenging the asserted utility under §101." (Emphasis added.)

Finally, the USPTO, in its legal overview, addresses some special considerations regarding asserted therapeutic or pharmacological utilities (Section III.) stating:

> The Federal courts have consistently reversed rejections by the Office asserting a lack of utility under §101 for inventions claiming a pharmacological or therapeutic utility where an applicant has provided evidence supporting such a utility. In view of this, Examiners should be particularly careful in their review of evidence provided in support of an asserted therapeutic or pharmacological utility."

Thus, where a credible pharmacological utility is asserted by an applicant, it must be assumed by the Examiner to be a true statement of utility unless the Examiner shows that one of skill in the art would find no rational scientific basis for the asserted utility. Further, it is important to distinguish "pharmacological activity" from "therapeutic activity". Pharmacological activity refers, essentially, to any biological activity. For example, a compound that is demonstrated, via *in vitro* or *in vivo* testing, to affect a biological function such as blood flow, hormone binding, enzyme operation, etc. *in vivo* has pharmacological activity. The CCPA has stated that, "Knowledge of the pharmacological activity of any compound is obviously beneficial to the public." Therefore, any pharmacological activity is practically useful.

Claims

The claims at issue are directed to screening methods for identifying compounds that inhibit the protease activity of a polypeptide by contacting a polypeptide of claims 1, 4, 123 or 124 with a substrate that is proteolytically cleaved by the polypeptide, and, either simultaneously, before or after, adding a test compound or plurality thereof. The amount of substrate cleaved in the presence of the test compound is measured and test compounds that decrease the amount of substrate cleaved compared to a control selected to identify candidate anti-tumor compounds that inhibit the activity of the polypeptides are identified. Hence, the

claims are directed to methods for screening for candidate compounds. The issue is whether such methods meet the threshold required for utility.

Analysis

The Examiner states the utility of a claimed method depends upon disclosure of a specific and substantial utility for a compound discovered, that there is no teaching of what an undisclosed compound detected by a claimed method "modulates", i.e., there is no specific or substantial utility for the "modulator", whether it inhibits or enhances protease activity. The claims are not directed to the compounds that are to be discovered but to the method of identifying compounds that inhibit the protease. The method for identification of candidate anti-tumor compounds has patentable utility.

The Examiner urges that the specification provides no nexus between the protease and any disease or physiological condition. First, this is a misstatement of the requisites for the threshold finding of utility; second, the specification does evidence such nexus; and third, the claims are directed to methods for screening compounds to identify candidate inhibitors of the protease, not to compounds. There is no need to demonstrate any pharmacological utility of any compounds. The claims are not directed to compounds nor to methods of treatment. Hence the issue is only whether one of skill in the art would find benefit from such assays, not whether any particular compound has therapeutic activity.

The Examiner comments that the cited case law is not relevant because the cited cases concern therapeutic utility. This is puzzling, since the Examiner is predicating the rejection on the alleged lack of utility of identified compounds. To assess credibility, the Examiner should follow the Patent Office's guidelines and first should determine if one skill in the art would consider the assertions of the applicant to have any reasonable scientific basis. If they do, they should not be challenged as not being credible. Only where they do not (e.g., if the assertion is "incredible in view of contemporary knowledge"), only then should the Examiner challenge the statement as not being credible. In this instance, the Examiner has not met his burden in establishing that the utility of the claimed methods is not credible. There is no evidence that asserting that methods for screening for compounds that inhibit activity of the MTSP7 protease to identify candidate anti-tumor agents is incredible in light of knowledge at the time of filing.

The Examiner has cited no references nor provided any reasons why one of skill in this art would doubt the credibility of the asserted utility. In the absence of such finding the Office has not met its initial burden in establishing a prima facie case of lack of utility. Hence the burden should not switch to applicant to demonstrate credibility. Nevertheless, the disclosure and teachings in the specification evidence the credibility of the utility of the claimed screening methods.

Teachings in the specification evidence that the utility of such methods is credible

The specification teaches that neoplastic diseases proliferate by the generation, increase and metastasis of a tumor mass. Cells that acquire such phenotypes often activate new genes and biochemical functions that are inactive or present at different levels in non-tumor cells (see for example, at pages 1-2). Proteases, especially cell surface proteases are implicated in tumor development because a hallmark of tumor development is the breakdown of the basement membrane by proteolytic and other enzymes (see for example, at page 2). The specification teaches that compounds that alter the activity of an MTSP7, particularly, inhibit it, are candidate anti-tumor agents. Further, The case law, including the Patent Office's guidelines, do nor require demonstration of clinical effectiveness, only demonstration that one of skill in the art would consider the method of screening for compounds that inhibit the activity of a protease to provide a benefit. Utility under 35 U.S.C. §101 is a threshold requirement.

The specification provides evidence that MTSP7 is differentially expressed in tumor cells and that proteases are recognized to be involved in tumor development and in neoplastic disease (which words appear in the specification).

For example, at page 4, the specification states:

> Serine proteases, including transmembrane serine proteases, have been implicated in processes involved in neoplastic development and progression. While the precise role of these proteases has not been elaborated, *serine proteases and inhibitors thereof are involved in the control of many intra- and extracellular physiological processes, including degradative actions in cancer cell invasion, metastatic spread, and neovascularization of tumors, that are involved in tumor progression.* It is believed that proteases are involved in the degradation of extracellular matrix (ECM) and contribute to tissue remodeling, and are necessary for cancer invasion and metastasis. The activity and/or expression of some proteases have been shown to correlate with tumor progression and development. [emphasis added]

Hence it is known to those of skill in the art that proteases and inhibitors thereof are involved in the control of processes in involved in cancer cell invasion, metastatic spread, and neovascularization of tumors (*i.e.*, tumorigenesis).

At page 11, the specification states:

> Also provided herein are methods of modulating the activity of the MTSP7 and screening for compounds that modulate, including inhibit, antagonize, agonize or otherwise alter the activity of the MTSP7.

At page 12-13 the specification states:

> Also provided are methods for screening for compounds that modulate the activity of MTSP7. The compounds are identified by contacting them with the MTSP7 or protease domain thereof and a substrate for the MTSP7. A change in the amount of substrate cleaved in the presence of the compounds compared to that in the absence of the compound indicates that the compound modulates the activity of the MTSP7. *Such compounds are selected for further analyses or for use to modulate the activity of the MTSP7, such as inhibitors or agonists*. The compounds can also be identified by contacting the substrates with a cell that expresses the MTSP7 or the extracellular domain or proteolytically active portion thereof. [emphasis added]

Thus, the specification states that methods for screening for compounds are candidates for use as inhibitors of MTSP7 are provided.

MTSP7 is a transmembrane protein with an extracellular protease domain that can play a role in proteolytic degradation at the cell surface as well as signal transduction (see for example, at page 4, lines 12-24 and at page 47, lines 16-29). The specification further explains (and demonstrates, see below) that MTSP7 levels differ in tumor and non-tumor cells (page 11, lines 5-12):

> MTSPs are of interest because they appear to be expressed and/or activated at different levels in tumor cells from normal cells, or have functional activity that is different in tumor cells from normal cells, such as by an alteration in a substrate therefor, or a cofactor. MTSP7 is of interest because it is expressed or is active in tumor cells.

The specification explains that MTSPs such as MTSP7 therefore are therapeutic targets (page 47, line 16 to page 48, line 2):

> The MTSP family is a target for therapeutic intervention and also some members can serve as diagnostic markers for tumor development, growth and/or progression. As discussed, the members of this family are involved in proteolytic processes that are implicated in tumor development, growth and/or progression. This implication is based upon their functions as proteolytic enzymes in processes related to ECM

degradative pathways. In addition, their levels of expression or level of activation or their apparent activity resulting from substrate levels or alterations in substrates and levels thereof differs in tumor cells and non-tumor cells in the same tissue. Hence, protocols and treatments that alter their activity, such as their proteolytic activities and roles in signal transduction, and/or their expression, such as by contacting them with a compound that modulates their activity and/or expression, could impact tumor development, growth and/or progression. Also, in some instances, the level of activation and/or expression can be altered in tumors, such as lung carcinoma, colon adenocarcinoma and ovarian carcinoma.

At page 13, the specification states:

> Also provided herein are modulators of the activity of MTSP7, especially the modulators obtained according to the screening methods provide herein. Such modulators can have use in treating cancerous conditions, and other neoplastic conditions.

Thus, the specification teaches that compounds identified by the screening methods have use in treating cancerous conditions.

At page 15, the specification states:

> Also, provided are methods for treating or preventing a tumor or cancer in a mammal by administering to a mammal an effective amount of an inhibitor of an MTSP7, whereby the tumor or cancer is treated or prevented. The MTSP7 inhibitor used in the treatment or for prophylaxis is administered with a pharmaceutically acceptable carrier or excipient. The mammal treated can be a human. The treatment or prevention method can additionally include administering an anti-cancer treatment or agent simultaneously with or subsequently or before administration of the MTSP7 inhibitor.

At page 16, the specification states:

> Methods of inhibiting tumor invasion or metastasis or treating a malignant or pre-malignant condition by administering an agent that inhibits activation of the zymogen form of MTSP7 or an activity of the activated form are provided. The conditions include, but are not limited to, a condition, such as a tumor, of the breast, cervix, prostate, lung, ovary or colon.

At page 71-71, the specification states:

> The single chain protease domains, as shown herein, can be used in a variety of methods to identify compounds that modulate the activity thereof. For MTSPs that exhibit higher activity or expression in tumor cells, compounds that inhibit the proteolytic activity are of particular interest. For any MTSPs that are active at lower levels in tumor cells, compounds or agents that enhance the activity are potentially of interest. *In all instances the identified compounds will include agents that are candidate cancer treatments.* [emphasis added]

At page 75, the specification states:

> The identified compounds are candidates or leads for identification of compounds for treatments of tumors and other disorders and diseases involving aberrant angiogenesis.

At page 156, in the Examples, the specification provides data demonstrating differential expression of MTSP7 in tumor cells:

> It is also highly expressed in lung carcinoma (A549 cell line), leukemia (K-562 cell line) and cervical carcinoma (HeLaS3 cell line).

Thus, the specification teaches that compounds that inhibit or otherwise modulate the activity of a an MTSP7 can be candidate compounds for treatment of a tumor or cancer (i.e., inhibit tumorigenesis). There is discussion and description in the specification describing the nexus between protease expression and cancer development and progression. There is disclosure in the specification that provides data evidencing differential expression of MTSP7 in tumor cells. Thus, specification establishes that proteases are known to have activities associated with the development and metastasis of tumors and shows that MTSP7 is expressed at high levels in tumor cells. The specification teaches that compounds that inhibit activity of MTSP7 are candidates or leads for identifying anti-tumor compounds.

In providing such assays, Applicant has made "a significant and useful contribution to the art, even though it may eventually appear that data establishes that an identified compound is without value in the treatment in humans" (In re Brana). Applicant has provided an assay to identify candidate anti-tumor compounds. There is no requirement to demonstrate therapeutic activity for any compound identified by the screening methods. Hence there is reason to conclude that one of skill in the art would consider that assays to identify compounds that inhibit the activity of MTSP7 possess the requisite patentable utility.

Applicant, having stated this credible utility in the specification, it's truth should not be questioned by the Examiner, unless a showing is made that those of skill in the art would have questioned the objective truth of the statement. As demonstrated, those of skill in the art clearly would not question this utility, as they espouse it. As discussed above, where a credible utility is asserted by an applicant, it must be assumed by the Examiner to be a true statement of utility, unless the Examiner shows that one of skill in the art would find no rational scientific basis for the asserted utility. The Examiner has not done so.

In summbary, The guidelines and case law establish that establishing a public benefit is sufficient utility. Knowledge of the pharmacological activity of any compound is

obviously beneficial to the public. Pharmacological activity is not therapeutic activity, but merely any biological activity or activity in an assay.

In summary, the instant application provides adequate evidence that the MTSPs are involved in processes that are involved in tumor development and metastasis. The application shows and states that MTSP7 is expressed in tumor cells. The assays provide identify compounds that inhibit MTSP7 activity. Such compounds are candidate anti-tumor agents by virtue of their inhibition of the activity of MTSP7. Therefore, the assays provide a publics benefit

THE REJECTION OF CLAIMS 65-67 AND 69-72 UNDER 35 U.S.C. §112, FIRST PARAGRAPH, LACK OF ENABLEMENT AS TO USE

Claims 65-67 and 69-72 are rejected for reasons of record under 35 U.S.C. § 112, first paragraph, for lack of enablement as to use because the claimed method allegedly is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed methods. This rejection is respectfully traversed.

As discussed above, the claimed methods possess patentable utility, and as such the rejection under 35 U.S.C. §112, first paragraph, is moot. Notwithstanding this, one of skill in the art clearly could practice the methods as claimed. The specification provides the recited MTSP7 polypeptides, describes test compounds in detail and practice of the screening assays (see, pages 83-112, which describes test compounds and the assays in great detail). Furthermore, the claims recite all steps of the methods necessary to practice them.

THE REJECTION OF CLAIMS 1, 2, 4-6, 10, 18, 19, 50-55, 59-61, 65-67, 69-72, and 117-122 UNDER 35 U.S.C. §112 FIRST PARAGRAPH

A. The written description rejection of claims 1, 2, 4-6, 9, 10, 18, 19, 50-55, 59-61, 65-67, 69-72, and 117-120

1. Claims 1, 2, 4-6, 9, 10, 18, 19, 50-55, 59-61, 65-67, 69-72, and 117-120 are rejected under 35 U.S.C. §112, first paragraph because it is alleged that the specification does not describe the subject matter in such a way as to convey to one skilled in the relevant art that the inventor(s) had possession of the claimed subject matter at the time the application was filed. In particular, it is alleged that the specification does not exemplify, describe, suggest or otherwise discuss preparation of divergent proteases that include as many as 10% of the amino acid positions that differ from the MTSP7 polypeptides set forth in the

application in SEQ ID NOS: 16 and 18. Responsive to Applicant's arguments, the instant Office Action urges that the specification only identifies the catalytic triad and a cysteine within the protease domain as identifying characteristics. Hence, it is alleged that identification of these features does not provide one of skill in the art sufficient guidence of the location or nature of the modifications in the polypeptides to evidence possession of the polypeptides as claimed.

It is respectfully submitted that this basis for rejection is rendered moot by the amendment herein. The claims as amended do not recite variations of 10% or 3% as previously pending. Applicant again emphasizes that the amendments herein are provided to advance claims to issuance, and not because Applicant concedes the propriety of the rejection.

2. New matter rejections

Claims 4, 6, 52-54, 65-67 and 69-72 are rejected under 35 U.S.C. § 112, firsf paragraph, as failing to comply with the written description requirement because the amendments to claims 4, 65 and 69 filed 9 February 2005 contain subject matter that is alleged not to be described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, there is no disclosure of a polypeptide comprising "an MTSP7 portion" that is "the only MTSP7 portion" of the polypeptide, or of a conjugate that comprises such a polypeptide, and there is no disclosure that a method of claims 65-67 and 69-72 identifies a 'modulator" that will "inhibit tumorigenesis"

a. Claim 4 and dependents – the MTSP7 portion

The Examiner also urges that recitation of of language that specifies that the claimed polypeptide contains only the protease domain of an MTSP7 is new matter. This rejection is respectfully traversed as it applies to rejected claim 4 and claim 4 as amended herein and claims dependent thereon.

Amended claim 4:

> A substantially purified single or two chain polypeptide, comprising an MTSP7 protease domain or comprising a catalytically active fragment thereof, wherein:
>
> said MTSP7 protease domain or catalytically active fragment thereof is the only MTSP7 portion of the single or two chain polypeptide; and

> the protease domain of MTSP7 has only the sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 17.

Relevant law

The written description requirement of 35 U. S. C. 112, first paragraph, can be satisfied without express or explicit disclosure of a later- claimed invention. See, In re Herschler, 591 693, 700, 200 USPQ 71 1, 717 (CCPA 1979):

> The claimed subject matter need not be described *in haec verba* to satisfy the description requirement. It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having skill in the pertinent art would recognize from the disclosure that appellants invented processes including those limitations." (citations omitted). See also Purdue Pharma L. P. v. Fauldinq, Inc., 230 1320, 1323, 56 1481, 1483 (Fed. Cir. 2000).

Also, the transitional phrases "comprising", "consisting essentially of" and "consisting of" define the scope of a claim with respect to what unrecited additional components or steps, if any, are excluded from the scope of the claim. nsitional phrases occur between the preamble of a claim and the body of the claim and are accorded their respective meanings only when the phrase is used as a transitional phrase. Hence, "comprising" when it appears as a transitional phrase, renders the claim open to additional components. When "comprising" appears elsewhere in the body of the claim, its meaning is subject to the standard rules of claim interpretation.

M PEP 2111.03 states and the case law supports the rule that the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and to those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976).

Hence, the Examiner's urging that the language "consisting essentially of" only applies to compositions is without basis in the law. The language, when used as a transition phrase, limits the scope of the claims to the specified materials and to those that do not materially affect the basic and novel characteristics of what is claimed. Thus, there is no reason why it cannot and does not apply to molecules.

Analysis

The original claims and application provide and claim a polypeptide that contains only the protease domain of MTSP7 and that can contain non-MTSP7 amino acid residues.

The original claims 1, 4 and 6 and description in the specification provide basis for this language and interpretation. Original claim 4 recites:

> 4. The polypeptide of claim 1, wherein:
> the MTSP7 portion of the polypeptide consists essentially of the protease domain of the MTSP7 or a catalytically active portion thereof.

Original claim 6 recites:

> 6. The substantially purified polypeptide of claim 1 that consists essentially of the protease domain of MTSP7 or a catalytically active portion of the protease domain of MTSP7.

Ooriginal claim 1 recites:

> A substantially purified single or two chain polypeptide, comprising the protease domain of a type-II membrane-type serine protease 7 (MTSP7) or a catalytically active portion thereof.

Hence original claim 4 is directed to:

> A substantially purified single or two chain polypeptide, comprising the protease domain of a type-II membrane-type serine protease 7 (MTSP7) or a catalytically active portion thereof, wherein the MTSP7 portion of the polypeptide consists essentially of the protease domain of the MTSP7 or a catalytically active portion thereof.

Original claim 6 is directed to:

> A substantially purified single or two chain polypeptide, comprising the protease domain of a type-II membrane-type serine protease 7 (MTSP7) or a catalytically active portion thereof, wherein the polypeptide consists essentially of the protease domain of MTSP7 or a catalytically active portion of the protease domain of MTSP7.

Thus, there is basis for claiming a polypeptide that comprises an MTSP portion is only the protease domain. There also is basis for a polypeptide that consist essentially of the protease domain.

The specification at page 28, defines what is meant by a recitation that a polypeptide consists essentially of a protease domain:

> As used herein, **recitation that a polypeptide consists essentially of** the protease domain **means** that the only MTSP portion of the polypeptide is a protease domain or a catalytically active portion thereof. The polypeptide can optionally, and generally will, include additional non-MTSP-derived sequences of amino acids.

Therefore, claim 4 as previously pending and as amended herein, finds finds basis in original claims, including original claims 1 and 4, and in the specification, which defines what is intendd.

Even assuming that consisting essentially of has its meaning as a transition phrase, a basic and novel characteristic of polypeptides of claim 4 and dependents is that the protease domain alone is sufficient for protease activity. This is apparent from the specification, which describes and demonstrates that the protease domain, without additional amino acids required for activation cleavage can be be used alone without more MTSP7 sequence in a variety of method.

Furthermore, as used in claim 4 (prior to amendment) "consisting essentially of" is not a transition phrase and should be interpreted according to the rules of claim construction. The specification states in the definition section on page 28 that "recitation that a polypeptide consists essentially of the protease domain **means** that the only MTSP portion of the polypeptide is a protease domain or a catalytically active portion thereof." Thus there is exact basis in the specification for a claim directed to a polypeptide that contains the protease domain as the only MTSP7 portion. As amended, the claim states that the protease domain portion of the polypeptide has only the sequence of amino acid encoded by SEQ ID No. 17.

b. Claims 65-72 – tumorigenesis

As discussed above, claims 65-72 find basis in the application as originally filed. As quoted above, the specification teaches that the screening methods identify compounds that inhibit MTSPs, including MTSP7, and that " members of this family are involved in proteolytic processes that are implicated in tumor development, growth and/or progression" (*i.e.*, tumorigenesis). The claims, however, are amended to recite that the screening methods identify anti-tumor compounds. The sections of the specification quoted above with reference to the utility rejection, are replete with references to use of the methods for isolation of compounds for treating cancers and tumors. Therefore, claims 65-72 find basis in the specification as originally filed.

c. The rejection of claims 1, 2, 4-6, 9, 10, 18, 19, 50-55, 59-61, 65-67, and 68-72 under U.S.C. § 112, for lack of enablement

Claims 1, 2, 4-6, 9, 10, 18, 19, 50-55, 59-61, 65-67, and 68-72 are rejected for lack of enablement because the specification is not enabling for any embodiment of a polypeptide comprising an MTSP7 protease domain that has an amino acid sequence diverging from SEQ

ID NO:18 by as many as 23 amino acids or diverging from SEQ ID NO:16 by as many as 44 amino acids. It is alleged that the specification does not show how or where such amino acid variation should be made in SEQ ID NOS:16 and 18. The Final Office Action contends that because the prior art does not identify proteins having a 10% sequence divergence and maintaining catalytic activity, it would be unpredictable how to make such changes in MTSP7 polypeptides and maintain activity.

In view of the amendments herein, it respectfully is submitted that the rejection is moot. As noted above, however, applicant does not concede that this rejection has merit nor has applicant conceded any issues. The claims are amended in order to permit allowable subject matter to proceed to issuance.

THE REJECTION OF CLAIMS UNDER 35 U.S.C. §112, Second Paragraph

A. The Office Action alleges that claims 4, 6, 52-55, 69, 117 and 118 are indefinite due to the recitation of "portion" multiple times in claim 4, where a portion allegedly can include another portion. Claims 6, 52-55, 69 and 177-118 are included in the rejection because they depend from claim 4. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks. Again, applicant is not conceding the propriety of the rejection, but has amended the claims to advance the application to allowance and to permit some subject matter to issue. The amendments herein render the grounds for this rejection moot.

Claim 4 as amended herein recites:

> 4. A substantially purified single or two chain polypeptide, comprising an MTSP7 protease domain or comprising a catalytically active fragment thereof, wherein:
>
> said MTSP7 protease domain or catalytically active fragment thereof is the only MTSP7 portion of the single or two chain polypeptide; and
>
> the protease domain of MTSP7 only has the sequence of amino acid residues encoded by the sequence of nucleotides set forth in SEQ ID No. 17.

The claim only recites the phrase "MTSP portion" once and it references the protease domain. In addition, the claim recites that the protease domain "only has" the "sequence of amino acids set encoded by the sequence of nucleotides set forth in SEQ ID No. 17." "Has" is closed language. Claim 4 as amended is directed to a polypeptide that comprises the

protease domain of MTSP7, where the protease domain is the only MTSP7 portion of the polypeptide.

B. Claims 1, 2, 4-6, 8-10, 18, 19, 50-55, 59-61, 65-67, 69-72 and 117-1 22 are allegedly indefinite because claims 1, 4 and 119-121 recite "serine protease activity", affecting claims 2, 5, 6, 8-10, 18, 19, 50-55, 59-61, 65-67, 69-72, 117 and 118 that depend from claims 1 and 4. The term "serine protease activity" is ambiguous, thus indefinite, because it fails to define the nature of the proteolytic activity described by the specification, which is a proteolytic activity with the peptide substrate S2366. A peptide may be cleaved by a variety of proteases, whether serine proteases, metalloproteases, or cysteine proteases, and the failure of the claims and the specification to identify what is intended by "serine protease activity" leaves the metes and bounds of the intended subject matter uncertain for the artisan and the public seeking to determine the scope of the claims. This rejection is respectfully traversed.

At page 15 of the specification, serine proteases are defined as:

> As used herein, serine protease refers to a diverse family of proteases wherein a serine residue is involved in the hydrolysis of proteins or peptides. The serine residue can be part of the catalytic triad mechanism, which includes a serine, a histidine and an aspartic acid in the catalysis, or be part of the hydroxyl/ε-amine or hydroxyl/α-amine catalytic dyad mechanism, which involves a serine and a lysine in the catalysis.

Hence, serine protease activity, which is well known to those of skill in the art, is described as the activity of a protease in which a serine residue is involved in the hydrolysis of proteins or peptides. Therefore, serine protease activity is not unclear, nor is there any basis to doubt that MTSP7 is a serine protease.

THE REJECTION OF CLAIMS 4, 6, 52-55, 69, 120 AND 122 UNDER 35 U.S.C. §102(e)(1)

Claims 4, 6, 52-55, 69, 120 and 122 are rejected under 35 U.S.C. §102(e)(1) as being anticipated by Alsobrook *et al.* (U.S. Patent Application No. 2003/0170630) because the human serine protease disclosed by Alsobrook *et al.* allegedly is identical to SEQ ID NO:18 and meets the limitation of clause (b) of claim 4 and claim 6 dependent thereon. It is further alleged that Alsobrook *et al.* discloses conjugates, attachment to surfaces and screening methods such as claimed in claims 52-55 and 69. Additionally, the Office Action alleges that Alsobrook *et al.* inherently anticipates claims 120 and 122 because it discloses recombinant

expression of proteases in eukaryotic cells that would allegedly result in activated cleavage and a two-chain protease. Reconsideration and withdrawal of these rejections are respectfully requested in view of the clarification of the claim language herein and the following remarks.

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

"Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the "'prior art'" . . .the [r]eference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings in the cited references. Such picking and choosing may be entirely proper when making a rejection of a §103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art, but it has no place in the making of a §102, anticipation rejection." (Emphasis in original). In re Arkey, Eardly, and Long, 455 F.2d 586, 172 USPQ 524 (CCPA, 1972).

The Claims

Claim 4 as amended is directed to a polypeptide that comprises the protease domain of MTSP7. The protease domain is the only MTSP portion of the polypeptide and has the

sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 17. The rejected claims depend from claim 4. Dependent claims 52-55 are directed to conjugates that contain the polypeptide of claim 4, and dependent claim 69 is directed to a method for screening.

Alsobrook *et al.*

Alsobrook *et al.* describes a human NOV1a protease that is 420 amino acids in length. The 420 amino acid sequence of NOV1 disclosed in Alsobrook *et al.* is different from the sequence of amino acids set forth in SEQ ID No. 16 herein at numerous positions (at least 91 positions). Furthermore, as discussed in previous responses, and accepted by the Examiner, Alsobrook *et al.* does not disclose a polypeptide the only contains the protease domain and nothing more or a polypeptide that contains the protease domain and no other MTSP7 portions. Alsobrook *et al.* also does not disclose conjugates nor screening assays for identifying compounds that inhibit MTSP7 and that are candidate anti-tumor compounds.

Hence, with respect to claim 4 and claims dependent thereon, Alsobrook *et al.* does not disclose a polypeptide where the only MTSP portion of the polypeptide is the MTSP7 protease domain or a catalytically active portion thereof where the protease domain has the sequence of amino acids encoded by the sequence of nucleotides set forth in SEQ ID No. 17. Therefore, Alsobrook *et al.* does not disclose all elements as claimed and does not anticipate claim 4 nor any claims dependent thereon, nor any pending claims.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,

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